

LEVEL II

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REPORT DOCUMENTATION PAGE

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1. REPORT NUMBER		2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) PGA-PLA Ureteral Replacements		5. TYPE OF REPORT & PERIOD COVERED Manuscript	
7. AUTHOR(s) COL Duane E. Cutright, MAJ William Green COL Emery A. Russell, LTC Marvin F. Grower		6. PERFORMING ORG. REPORT NUMBER (12)	
9. PERFORMING ORGANIZATION NAME AND ADDRESS U. S. Army Institute of Dental Research Walter Reed Army Medical Center Washington, DC 20012		8. CONTRACT OR GRANT NUMBER(s)	
11. CONTROLLING OFFICE NAME AND ADDRESS U. S. Army Medical Research & Development Command HQDA (SGRD-AJ) Ft. Detrick, Frederick, MD 21701		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS	
14. MONITORING AGENCY NAME & ADDRESS (If different from Controlling Office)		12. REPORT DATE 25 August 1978	
		13. NUMBER OF PAGES 12	
		15. SECURITY CLASS. (of this report) UNCLASSIFIED	
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE	
16. DISTRIBUTION STATEMENT (of this Report) This document has been approved for public release and sale; its distribution is unlimited.			
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)			
18. SUPPLEMENTARY NOTES None			
19. KEY WORDS (Continue on reverse side if necessary and identify by block number)			
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary experimentation in rats and dogs, demonstrates the potential for ureteral regeneration employing polyglycolic-poly-lactic acid cylinders. Although prolonged patency was not consistently achieved, potential for predictable biodegradation with simultaneous transitional cell and smooth muscle ingrowth holds promise for future work.			

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POLYGLYCOLIC AND POLYLACTIC ACID COPOLYMERS
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Abstract

Preliminary experimentation in rats and dogs, demonstrates the potential for ureteral regeneration employing polyglycolic-polylactic acid cylinders. Although prolonged patency was not consistently achieved, potential for predictable biodegradation with simultaneous transitional cell and smooth muscle ingrowth holds promise for future work.

Optimal reconstruction of the ureter after extensive injury continues to challenge the most skilled urologist. Innumerable foreign materials have been employed experimentally to bridge ureteral defects. These have included glass (1), silicone (2), teflon (3), polyethylene (4), and metallic compounds (5,6). Unfortunately each has been poorly tolerated in the host animal. Significant problems have included infection, calculus formation, urinary leakage, dislodgement and eventual hydronephrosis with obstruction.

With the failure of foreign materials, researchers next turned to live tissue grafts attempting to improve results. Autologous tissues have included skin (7), appendix (8), fallopian tube (9), veins (10) and arteries (11). In the clinical practice of urology, only three techniques are of proven value: the Psoas hitch, the Boari flap and intestinal interposition.

Recent studies (12,13,14) have reported success in both laboratory animals and humans of implanting silicone tubing with dacron-felt cuffs. The cuffs have permitted ingrowth of tissue creating a seal between normal ureter and the prosthesis. Although leakage and infection have occurred in some cases, approximately 50% of reconstructed units have demonstrated

satisfactory results. Foreign materials exposed to urine within the body are prone to the development of calculi, infection and obstruction. In an attempt to avoid these complications, we hypothesized the use of biodegradable materials to initiate ureteral regeneration. To this end an initial study was performed to determine if tissue would replace a biodegradable cylinder of a copolymer composed of 50% polylactic and 50% polyglycolic acid, resulting in a hollow tube of fibrous connective tissue simulating a ureter. The cylinders were machined from rods composed of 50% polylactic acid (PLA) and 50% polyglycolic acid (PGA). Each cylinder measured 2 mm inside diameter with a 1 mm thick wall. A non-resorbable teflon mandril was machined to fit snugly inside the cylinder, thus assuring patency of the developing connective tissue cylinder

Twelve adult rats were anesthetized with intraperitoneal sodium thiopental. After shaving and antiseptic cleansing, 1 cm. incisions were made in each side of the abdomen and pockets created in the subcutaneous tissue by blunt dissection. A PGA-PLA cylinder with teflon mandril was implanted on each side. The wounds were closed with 3-0 chromic sutures. Following uneventful recovery, the animals were sacrificed at intervals from 2 to 9 weeks. The area of the implants including the teflon mandrils was dissected free, placed in 10% buffered formalin, grossed, embedded, sectioned at 6 microns and stained with hematoxylin and eosin.

The initial feasibility study demonstrated the rapid degradation and high tissue tolerance previously described by Cutright et al for various copolymers (15). Histopathologic examination of the slides revealed

degradation being completed by 8 weeks. There was minimal foreign-body tissue reaction accompanying the degradation. A thin but dense connective sheath with abundant blood supply developed around the teflon mandril. The orientation of the connective tissue fibers was without pattern but appeared to be oriented according to the structure of the copolymer itself.

Method & Materials

In the primary study in dogs, hollow cylinders of PGA-PLA were fabricated with smooth lumen and with walls having longitudinal and circular fibers in alternate layers. The layers were designed to degrade at slightly different times by varying the proportions of PGA to PLA as described by Cutright⁽¹⁵⁾. The smooth lumen was formed by dipping a 3.8 mm. mandril in 100% PLA. This gave a porous film approximately 100 microns thick. Alternate layers of 50/50 PGA/PLA copolymer and 100% PLA were then sprayed on the inner layer while rotating the cylinder at approximately 50-100 rpm. Outer layers were alternately applied with very slow rotation (10-25 rpm) with a horizontal movement of the spray to give nearly longitudinal fiber arrangement. These tubes measuring 3.8 mm. inside diameter with 1.5 mm. thick walls and were sterilized with ethylene oxide.

Six mongrel dogs weighing 20 - 30 kilograms underwent intravenous pyelograms (IVP) to confirm the presence of two normally functioning renal units. Each was placed under general endotracheal anesthesia with nitrous oxide, halothane and oxygen. The abdomen was shaved and scrubbed with antiseptic solution. An 8 cm upper abdominal incision was made and the peritoneal cavity was entered. Reflection of the small bowel to the right permitted ready access to the left ureter. A 2 cm. segment of the upper third of the ureter was excised and sent for pathologic identification.

A number five french polyethylene stent was passed through the distal ureter into the bladder, brought out through the bladder wall, knotted and implanted into the subcutaneous tissue for later removal. Additional side holes were made in the portion which was to remain in the bladder to allow better drainage. The proximal end of the stent was brought through the hollow PGA-PLA graft and placed in the renal pelvis. The graft was anastomosed to the ends of the transected ureter with interrupted 5-0 Dexon sutures. Care was taken to surround the graft with retroperitoneal fat in an attempt to minimize adhesions. No external drainage was used and the midline incision was closed anatomically.

Postoperatively the dogs received therapeutic doses of Ancef* I.M. for the first 14 days. On the 14th day each dog was anesthetized with intravenous sodium pentothal and an IVP was performed. During the same anesthesia, a small incision was made over the knotted end of the ureteral stent and the stent was withdrawn. Intravenous pyelograms were obtained at intervals of 2-3-6 months to follow the progress of each graft. The animals were sacrificed at 2,3 and 6 months after surgery. The kidney and ureter were removed in toto, and fixed in 10% buffered formalin. The tissue was then grossed, embedded, sectioned at 6 microns and stained with hematoxylin and eosin. Selective blocks were stained with Masson Trichrome stain and PTH stain for identification of smooth muscle.

Results

The intravenous pyelogram of each animal two weeks after surgery with the stent in place showed evidence of partial ureteral obstruction. Urinary extravasation with urinoma was seen in one dog which promptly resolved after removal of the stent. IVP's performed after removal of the stents all showed

*Smith, Kline and French Brand of Sterile Cefazolin Sodium.

progressive obstruction with delayed excretion of the contrast material. Only one graft remained patent until the animal was sacrificed at 6 months. On gross examination, each renal unit demonstrated hydronephrosis and ureteral dilation proximal to the area of the graft. At the time of initial operation on the sixth animal, the ureter was found to be of very small caliber and the stent could not be employed. The anastomosis was done in routine fashion; however the postoperative IVP at two weeks showed total obstruction and hydronephrosis.

Histology Results

The vasofibroblastic response replacing the copolymer, partially rimmed the graft site lumen at 2 months (Figure 1) and completely filled it at 6 months. This proliferating tissue divided the lumen into many channels as early as 3 months (Figure 4). Many of these channels appeared to be patent and covered by urothelium at six months.

Immediately following the connective tissue proliferation as seen in the 2 month samples the urothelium continued to proliferate over the surface of the reparative tissue. The six months samples showed urothelial coverage of most connective tissue septae within the graft site lumen. (Figure 5). The formation of bone within the walls of the ureter (Figure 3) was variable in amount but present in all time samples. Occasional trabeculae were ringed by osteoblasts. The bone formation was found both distal and mesial to the graft.

The tissue reaction to the copolymer in all time samples, was primarily one of minimal inflammation, vasofibroblastic proliferation, the presence of phagocytic cells and an occasional giant cell (Figures 2 & 5). The proliferating connective tissue tended to become oriented along the planes and fibers

of the original copolymer. The copolymer disappeared slowly and at six months was mostly eliminated as evidenced by the scattered copolymer.

The connective tissue wall surrounding the graft measured from 50 to 180 microns in thickness at 2 months, and increased to 100 to 220 microns by 6 months. Smooth muscle cells appeared to proliferate into the area from the smooth muscle present in the cut ends of the ureter (Figure 6).

Discussion

Several authors have shown that Dexon and Vicryl sutures degrade by hydrolysis in a predictable fashion. Dexon is composed of 100% PGA, Vicryl is 90% PGA and 10% PLA. Documentation of the duration, sequence and fate of various copolymers as they degrade in tissue have been published⁽¹⁵⁾. These findings have shown that both give 100% PGA and pure 100% PLA degrade slowest while a copolymer of 50% PLA and 50% PGA degrades fastest. This allows the tailoring or customizing of degradation times according to the surgical requirement by varying the composition.

The authors theorized that the excellent tissue tolerance, controlled degradability and initial strength of these material combinations should make ureteral regeneration possible. Connective tissue can be expected to follow the pattern of the synthetic fibers and it was anticipated that smooth muscle would regenerate from the ends of the ureteral walls as demonstrated by Brothers et al using dacron grafts⁽¹⁶⁾.

This experiment has shown that a fibrous connective tissue sheath is formed and increases in thickness with degradation of the copolymer. It has also been shown that transitional epithelium proliferates and lines the segments of the regenerating ureter. The orientation of the connective tissue fibers somewhat follows the orientation of the copolymer fibers therefore simulating the layers of the wall of the normal ureter. It further appears that smooth muscle slowly invades the wall of the graft site from the margins of the normal ureter.

Thus all the components of a regenerated ureter appear to form with the degradation of the copolymer and its replacement by urothelial covered connective tissue.

The problem remaining appears to be the too rapid strength loss of the framework of the copolymer implant allowing the collapse of the implant into the lumen where it is then replaced with reparative tissue.

It appears totally feasible to keep the lumen patent for a sufficient period of time to allow the formation of a connective tissue cylinder lined by urothelium. Such a newly formed organ could function as a normal ureter. The peristaltic conduction of urine could return if no foreign body remains within the wall of the regenerated segment.

The authors believe that a more successful graft can be fabricated. This would involve a framework of slower degrading material to give stability and strength over a longer period of time. This would avoid the tendency of the graft to rapidly soften and collapse obstructing the Lumen. The spray spin application for this new graft would be similar to that described in the present experiment. This combination would allow time for connective tissue proliferation and transitional epithelial regeneration thereby creating a urothelial lined tube before loss of strength of the implant. Employment of this type of graft stent will be the basis for a future experiment.

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Legends

Figure #1 Two month postoperative graft site

The connective tissue wall (a) completely surrounds the copolymer. Just inside the connective tissue capsule (b) the first ingrowth of vasofibroblastic tissue can be seen. The lumen exhibits many clear spaces marked where the copolymer dissolved away during tissue processing.

The loose tissue outside the capsule is primarily fat which was used to surround the graft. X44

Figure #2 Two month postoperative graft site

A high power view of the capsule area showing (a) fat cells (b) Capsule (c) vasofibroblastic ingrowth into the lumen. X64

Figure #3 Two month postoperative graft site

The urothelial lining of the proximal ureter is shown at (a) with the boney trabeculae appearing immediately subjacent to it. 56X

Figure #4 Three month postoperative graft site

Low power view of the graft site lumen. The proliferating connective tissue has partially divided the lumen into segments. Channels lined by a thin layer of urothelium appear within the partially filled lumen. X40

Figure #5 Six month postoperative graft site

View of the original graft lumen showing degradation still continuing and several channels lined by urothelium such as seen at (a). The typically mild tissue reactive can be seen at (b). X64

Figure #6 Six month postoperative graft site

Cells resembling smooth muscle cells (a) and originating from overlying smooth muscle proliferate into the graft site. X120

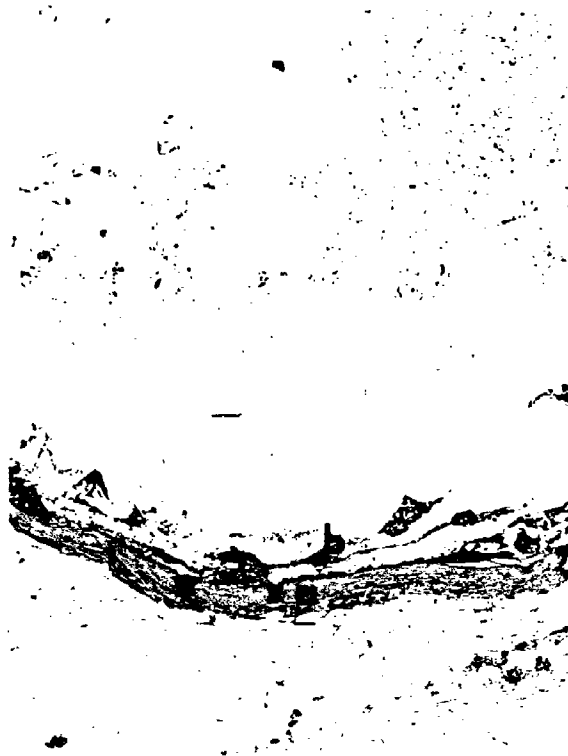
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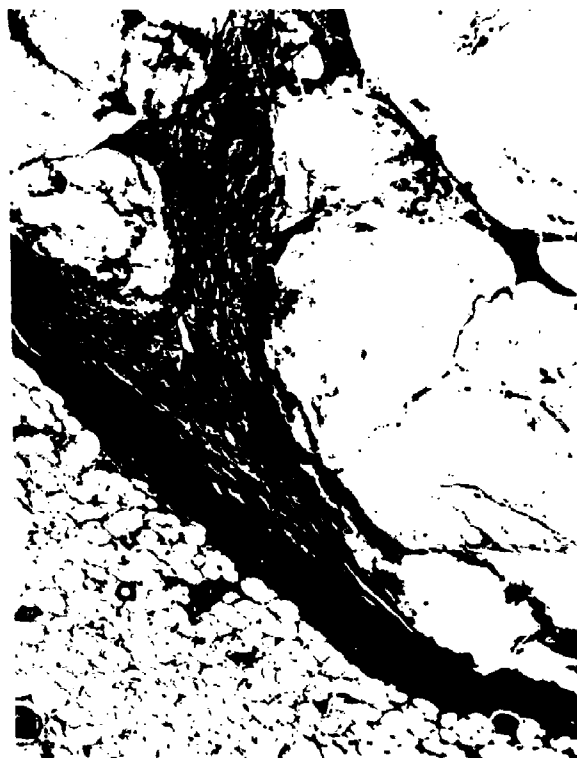
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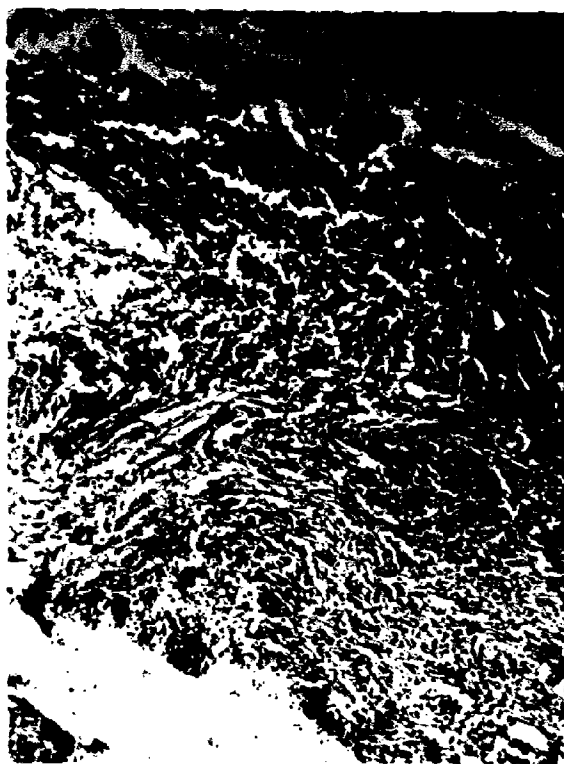


Figure 6